# Accelerated Approval

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# Highlights

- Approval with restrictions/conditions
- Serious/life threatening
- Advance over available therapy
- Effect on surrogate or other clinical endpoint
  - reasonably likely to predict clinical [or ultimate clinical] benefit
- Applicant conduct studies post approval to very and describe benefit

# Post marketing studies

- Required
- Ordinarily already underway
- Due Diligence
- Agency MAY withdraw approval
  - PM study fails to verify
  - Failure of due diligence
  - Part 15 hearing

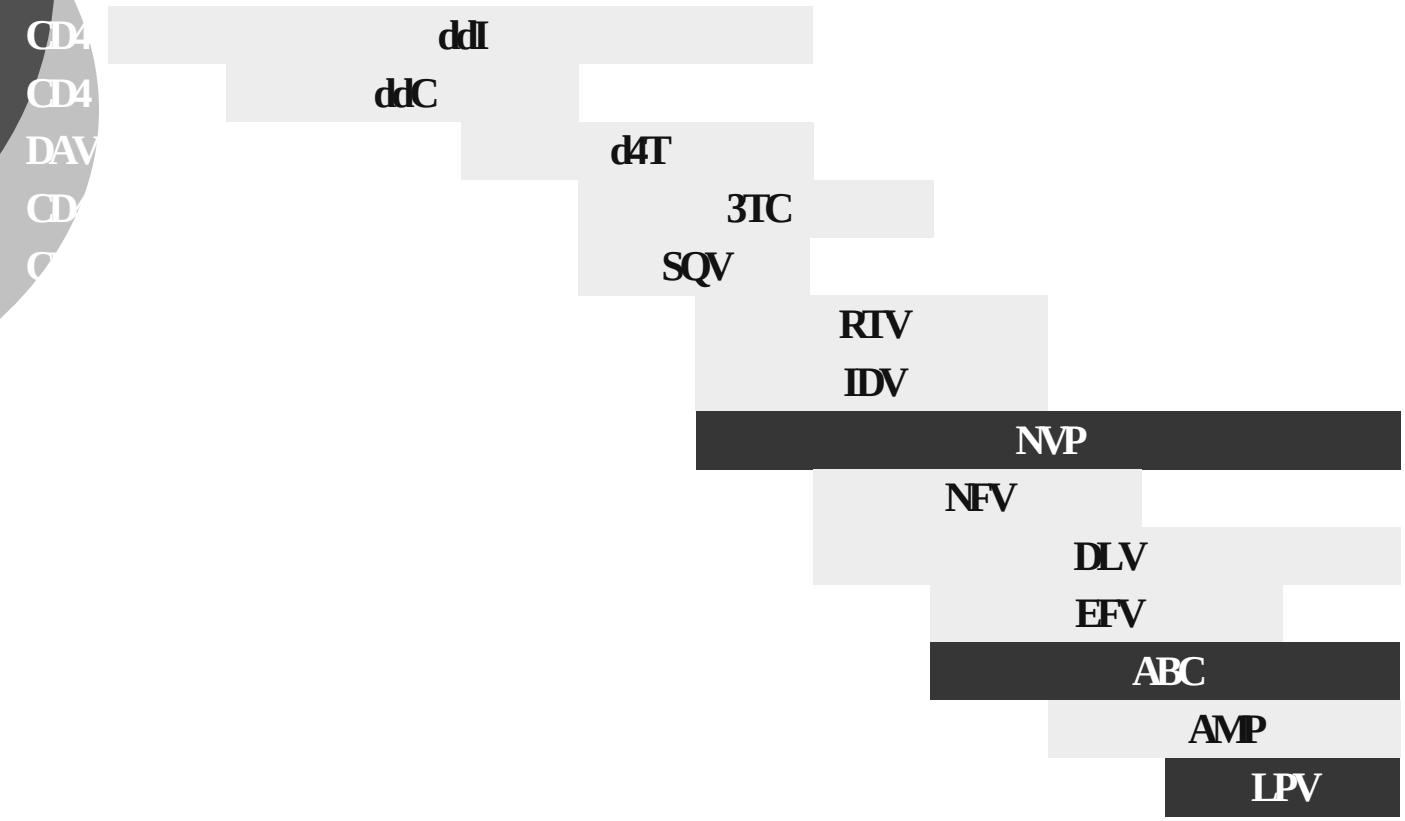
- 21 CFR 601.40-46, Subpart E or 21 CFR 314.500-560, Subpart H
- Final Rule Dec. 11, 1992 (57 FR 58942)
- Guidance for Industry- Fast Track Drug Development Programs Sept., 1998

# AA in HIV/AIDS

- Change in paradigm:
  - combination anti-viral therapy
  - sensitive viral assays
- Clinical endpoints no longer necessary or feasible
- Treatment-induced decreases in plasma RNA highly predictive of meaningful clinical benefit
  - basis for either regular or accelerated
  - short term reductions in viral load surrogate

- Antiretroviral drugs Using Plasma HIV RNA measurements – Clinical Considerations for Accelerated and Traditional Approval – Oct. 2002

# HIV/AIDS: Accelerated to Traditional Approval: Time and Endpoints



# Endpoints for Approval in Oncology

- Direct benefit
  - Overall survival
  - Improvement in tumor related sx
- Surrogates – DFS, ORR, PFS
  - Accepted as indicators of clinical benefit
    - Regular Approval
  - Reasonably likely to represent benefit
    - Accelerated Approval with PM studies

- Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics May 2005

# Oncology Drugs

- Survey 1990-2002
- 71 approvals – 57 RA, 14 AA
- 68% - endpoints other than survival
- Response rates -
  - 26/57 regular
  - 12/14 accelerated

J Johnson et al JCO 21 (7) 2003

# Issues in use of AA

- Difficulties identifying a reasonable surrogate endpoint
  - Rare diseases, ideal if natural history data available
  - Confirmatory trial might fail to show benefit
- Confirmatory trials may result in unacceptable risk/benefit)

# Iressa – initial trial

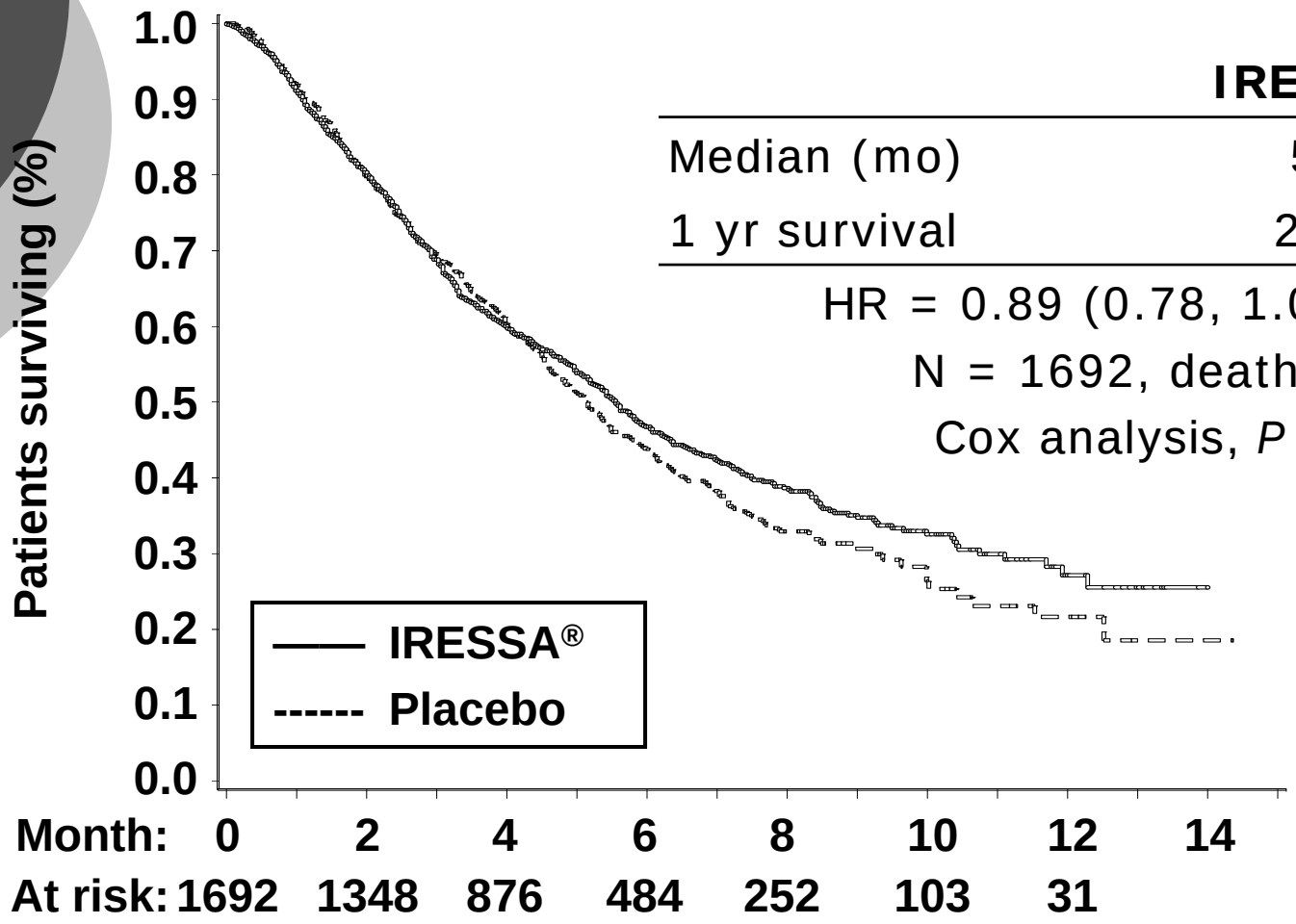
**Evaluable Patients**

**Table 2: Efficacy Results**

| | 250 mg N=66 | 500 mg (N=76) | Combined (N=142) |
|---|---|---|---|
| **Objective Tumor Response Rate (%)** | **13.6** | **7.9** | **10.6** |
| **95% CI (%)** | **6.4-24.3** | **3.0-16.4** | **6.0-16.8** |
| **Median Duration of Objective** | | | |
| **Response (months)** | **8.9** | **4.5** | **7.0** |
| **Range (months)** | **4.6-18.6 +** | **4.4-7.6** | **4.4-18.6 +** |

**+ =data are ongoing**

# Iressa – confirmatory trial
# Overall Survival




| | IRESSA® | Placebo |
|---|---|---|
| Median (mo) | 5.6 | 5.1 |
| 1 yr survival | 27% | 22% |

HR = 0.89 (0.78, 1.03), *P* = .11

N = 1692, deaths = 969

Cox analysis, *P* = .042

# Significant Improvement In Objective Response Rate

| | Patients, % (n/N) | | Odds ratio | |
|---|---|---|---|---|
| | **IRESSA®** | **Placebo** | **(95% CI)** | ***P* value** |
| Objective response rate | **7.7% (74/961)** | **1.2% (6/483)** | **7.03 (3.0, 16.4)** | **< .0001** |

## Table 2. 13-Month Clinical and 1-Year MRI Endpoints Add-On Study

| | TYSABRI® plus AVONEX® n=589 | | Placebo plus AVONEX® n=582 |
|---|---|---|---|
| **Clinical Endpoints** | | | |
| **Annualized relapse rate** | **0.36** | | **0.78** |
| **Relative reduction (percentage)** | | **54%** | |
| **Percentage of patients remaining relapse-free** | **67%** | | **46%** |

# Issues – Confirmatory Trial

- Ordinarily underway
  - Ideal - same trial - ex HIV/AIDS, MS
  - Cancer setting may entail NEW trial
- PLAN ahead
- Difficulty in conducting controlled once marketed
- Recent criticism re: lack of due diligence